system that includes succinic dehydrogenase plus enzymes in the cytochrome chain). Similarly, cytochrome *c* was supplied to the same fraction to obtain a measure for cytochrome oxidase. They then divided the amount of activity in a fraction with that from the initial extract. They reported that over three experiments on average 70% of the cytochrome oxidase activity and 74% of the succinoxidase activity was found in the large granule fraction, while less than 4% of the cytochrome oxidase activity and 7% of the succinoxidase activity was found in the microsome fraction (Hogeboom et al., 1946). They attributed the bit of activity in the microsome fraction to large granules or large granule fragments that corrupted it, and claimed that dark-field microscopic examination of the microsome fraction indicated the presence of a sufficient number of large granules to support this explanation. They traced most of the remaining activity of these enzymes to large granules in sediments that were discarded in the process of purifying the different fractions.

Whereas prior to the war the team was satisfied to determine what amount of the activity associated with an enzyme could be found in a given fraction, they now sought to link the activity of a given enzyme with only one fraction. This was the beginning of the one enzyme–one fraction approach to interpreting cell fractionation results discussed in Chapter 4. Adopting this approach, they claimed that "Taken together, these observations suggest that the cytochrome oxidase and succinoxidase systems . . . are entirely localized in the so called large granules" (Hogeboom et al., 1946, p. 626).

Subsequent to this research, two additional investigators joined the laboratory, Walter Schneider and George Palade. Schneider had completed his Ph.D. at one of the top biochemistry departments in the U.S., the University of Wisconsin, in 1945. Palade, a native of Romania, had studied medicine at the University of Bucharest, where he carried out physiological research on the kidneys of dolphins. During the war, he taught at the Department of Anatomy at the University of Bucharest, then emigrated in 1946 to New York City. There he first worked with Robert Chambers at New York University on cellular membranes but, upon seeing Claude's first micrographs (discussed below), started to volunteer in Claude's laboratory.

Together Hogeboom, Schneider, and Palade continued the investigations into the biochemistry of cell fractions.[17] A serious shortcoming of the earlier

[17] While his colleagues were refining the techniques for identifying enzymes with particular cell fractions, Claude pursued the question of whether the large granule fraction could itself be differentially fractionated. This would soon become a major endeavor of biochemists (see Chapter 6), but as early as Claude (1946), he reported separating a small particle component from mitochondria containing most of the ribose nucleic acid associated with large granules. He claimed these small particles from within mitochondria could be identified with elements approximately